Periodic Fevers in Children: Solving the puzzle leading toward treatment

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Learning Objectives

• Identify Periodic Fever Syndromes as autoinflammatory diseases
• Identify common presenting symptoms seen in Periodic Fever syndromes
• Discuss initial workup the PNP can initiate for a child with recurring non-infectious fevers
• Discuss when to refer patients with Periodic Fever symptoms to rheumatology and targeted treatments

Periodic Fever Syndromes

• Periodic Fever syndrome is a general term describing a group of diseases. Does not refer to a single disease, nor is it a specific diagnosis.
• Periodic fever syndrome refers to several different autoinflammatory diseases that have similar symptoms—the primary symptom being a recurrent fever for which no infectious cause can be found.
• Over time the child develops a pattern of recurrent fevers, often accompanied by a range of other non-infectious symptoms.

Our Immune System

Our immune system is typically divided into two categories: Innate and Adaptive. The overall function of our immune system is to protect us and keep us healthy.

Innate Immune System

Is a nonspecific defense mechanism that comes into play immediately or within hours of an antigen’s appearance in the body. These defense mechanisms include physical barriers such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body. The innate immune response is activated by chemical properties of the antigen.

Adaptive Immune System

The adaptive immune response is more complex than the innate. The antigen first must be processed and recognized. Once an antigen has been recognized, the adaptive immune system creates an army of immune cells specifically designed to attack that antigen. Adaptive immunity also includes a “memory” that makes future responses against a specific antigen more efficient.

Innate Immune System

• The innate immune system uses white blood cells and acute inflammation to attack pathogens. The innate immune system may be activated by triggers, but in some autoinflammatory diseases, the genetic mutation causing the disease makes certain danger sensors in cells to become frequently, or even continuously activated. These activated molecules in the cell join with other molecules to induce inflammation.
• Fever is a primary symptom of an activated innate immune system. This chronic activation of the innate immune system can lead to systemic inflammation that occurs throughout the body.
**Autoinflammatory diseases**
- Autoinflammatory diseases are caused by a malfunction in the innate immune system. This malfunction leads to an over active immune system. This over activation causes severe systemic inflammation throughout the body.
- Many autoinflammatory diseases tend to have frequent recurring fevers as the most obvious symptom. The fevers are often cyclic in nature, coming and going in some cases erratically and in some cases more predictably.
- The inflammation is often general and not targeted to one area of the body, meaning that from the start, the inflammation can occur anywhere in the body and is not limited to a specific organ.

**Periodic Fever Syndromes**
- Are Autoinflammatory diseases, many are related to a genetic mutations
- They are not contagious conditions and are rare diseases.
- Each specific type of periodic fever syndrome has its own set of common symptoms presenting along with a high temperature during attacks.
- Symptoms do vary among different autoinflammatory diseases and even from patient to patient, however there are many symptoms that occur in a number of these diseases during flares.

**Common Symptoms of Periodic Fever Syndromes**
Fever accompanied by some of the following symptoms
- Rash
- Headache
- Abdominal pain, Vomiting, Diarrhea & Constipation
- Conjunctivitis
- Mouth ulcers
- Cervical lymphadenopathy
- Joint pains, or arthritis
- Fatigue
- Abnormal blood test results during flares of symptoms: high WBC & high CRP, ESR
- Serositis (pericarditis, pleurisy)

**Symptoms seen in PFAPA**
- First Described in 1987 by Dr Marshall
- Most common Periodic Fever Syndrome
- No known genetic gene
- No known cause
- Affects all races, seen in younger children 2-5 years
- Fever and symptoms lasting 3-6 days, recurring every 21-28 days. Extremely predictable, patients are symptom-free between flares. No specific triggers have been identified—flares come at regular intervals

**PFAPA : aphthous stomatitis, pharyngitis, and cervical adenitis**
- Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
- Familial Mediterranean Fever, also known as Familial Hibernian Fever
- Tumor necrosis factor associated periodic syndrome
- Hyperimmunoglobulin D syndrome , also called Mevalonate Kinase Associated Periodic Fever Syndrome

**Periodic Fevers to be discussed for this presentation**
- PFAPA Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
- FMF Familial Mediterranean Fever
- TRAPS Tumor necrosis factor associated periodic syndrome
- HIDS Hyperimmunoglobulin D syndrome

**Symptoms:**
- High fevers (103-104) present with acute onset and can last for 3-6 days, with chills and malaise
- Aphthous ulcers (stomatitis), and pharyngitis with exudate, is classic (rapid streps will be negative, no active infection)
- Abdominal pain, and diarrhea are often present
- Cervical adenopathy
- Arthralgias, and fatigue, no arthritis on exam
- Patients are symptom-free between PFAPA flares.
**Working up a Fever in kids**

- Keep fever log and accurate history of symptoms
- Complete Physical exam to rule out an infectious process
- CBC, ESR, CRP
- Inflammatory markers ESR, CRP, high during attacks, then return to normal between flares
- Once pattern established refer to rheumatology for review and genetic testing. No known gene for PFAPA, however gene testing done as symptoms may mimic other periodic fever syndromes

**Diagnostic criteria of PFAPA per UpToDate**

- At least 3 episodes of fevers lasting no more than 5 days that occur at regular intervals. It’s noted that, “For individual patients, intervals between attacks are nearly identical within a range of three to six weeks, and the symptoms with each episode are identical.”
- Pharyngitis with swollen cervical lymph nodes and/or with mouth ulcers.
- Normal growth and no symptoms between flares.
- Resolution of symptoms with a single dose of prednisone.

**PFAPA Case study**

- LK is a 19 month old male referred to rheumatology for persistent fevers. HX of recurrent fevers since 6 months of age, with fevers every 6-8 weeks initially, now every 4 weeks. Fevers are usually 102-104. Over the past 13 months has had several episodes of tonsillitis, rapid streps negative. In addition to fever symptoms consist of drooling, decreased appetite, diarrhea, bad breath and irritable. Has had an extensive work up by PMD, ENT, and Allergy. Leo has seen ENT and they agree he has recurrent tonsillitis but will not take out his tonsils as he is too young (needs to be 3 or 30 lbs). Increased risk of adverse events if surgery done at a very young age

**Case study PFAPA**

- Work up in the past has included numerous rapid streps all negative, CXR normal, elevated ESR, CRP with fever which return to normal in between episodes.
- PE: normal at my exam, not experiencing a fever episode
- Plan: obtain prior authorization from health insurance for Genetic Fever panel
- Genetic Fever panel done, no mutation identified
- Treatment
  - single dose of prednisone of 12 mg (1mg/kg) with the start of each fever episode

**Treatment for PFAPA**

- There is no specific treatment to cure PFAPA.
- The aim of treatment is to control symptoms during the episodes of fever, to shorten the duration of episodes, and in some children to prevent attacks from occurring.
- The fever does not usually respond well to Tylenol or nonsteroidal anti-inflammatory drugs.
- In most children, the disease will resolve by itself without treatment, Children usually out grow the condition in the second decade of life
Treatment

Mediations
- A single dose of low dose prednisone (1-2 mg/kg) given when symptoms first appear, has been shown to shorten an episode and sometimes even end the episode.
- However, the interval between episodes may also be shortened with this treatment, and the next episode may occur earlier than expected.
- Colchicine at a dose of 20-40 mg/kg/day may prevent attacks from occurring.
- Colchicine 0.5-1 mg/day, will prevent future flares

Surgery
- In patients with very frequent attacks, a tonsillectomy maybe considered

Genetic Fever panel

- Genes identified by this panel
  - ELANE (ELA2), LPIN2, MEFV, MVK, NLRP3 (CIA5), PSTPIP1, TNFRSF1A
- Disorders identified in this genetic panel
  - Chronic Infantile Neurologic Cutaneous and Articular Syndrome
  - Cyclic Neutropenia
  - Familial Cold Autoinflammatory Syndrome
  - Familial Cold Urticaria syndrome
  - Familial Hibernian Fever
  - Familial Mediterranean Fever
  - Hyper-IgD Syndrome
  - Majeed Syndrome
  - Muckle-Wells Syndrome
  - Neonatal Onset Multisystem Inflammatory Disease
  - Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne Syndrome
  - TNF Receptor-Associated Periodic Syndrome

Cost of Genetic testing

- Genetic Testing
  - GeneDX Lab approximately $5000.00
  - MMG labs approximately $3000.00
  - Invitae is a private commercial lab $475.00
  - this company will send a lab technician to the home

Familial Mediterranean Fever FMF

- Most common monogenic autoinflammatory syndrome, resulting from autosomal recessive mutation in the Mediterranean Fever (MEFV) locus on chromosome 16

- In FMF children must inherit two abnormal copies of the MEFV gene - one from the mother and one from the father. The parents are then called carriers. Carriers are usually asymptomatic

- If one child has the disease and the parents are carriers, there is a 25% chance that another child will get FMF. If one child and one of the parents have FMF, there is a 50% chance of another child getting FMF.
FMF

- FMF is more common in certain ethnic groups, those whose ancestry was around the Mediterranean Sea, which include Armenians, Turks, Arabs, and Jews. Within these ethnic groups 1 out of 5-7 people can be a carrier of the MEFV mutation.
- More recently, however, FMF has been diagnosed in people from many other ethnic backgrounds.
- Attacks of FMF begin before the age of 20 in 90% of patients. In 75% of patients, fever appears before the age of 10 years.
- It is a chronic life-long disease and there is no known cure. Fortunately, there are good medications to control the disease.

The MEFV gene affects a protein called pyrin. Pyrin plays a role in the control of inflammation. When MEFV gene does not work correctly, inflammation occurs and patients experience episodes of fever and pain as a result.

FMF

- Infection, trauma, strenuous exercise, heavy menstrual periods and psychologic stress may trigger episodes of FMF fever and related symptoms.

Symptoms seen in FMF

- Recurrent high fevers (103-104) with acute onset for 1-3 days
- Abdominal pain
- Chest pain
- Joint pain/arthritis
- Fatigue/malaise

Work up for FMF

- Keep fever log and accurate history of symptoms
- Complete Physical to rule out an infectious process
- CBC, ESR, CRP
- Inflammatory markers ESR, CRP, high during attacks, then return to normal between flares
- Once pattern established refer to rheumatology for review and genetic testing

Case Study FMF

- AA is a 3 year old male referred to rheumatology for recurring fevers which started at 1 year of age. He would develop episodes of fever, abdominal pain and knee pain. Had knee pain with most episodes however no arthritis. He would occasionally vomit, have decreased appetite, energy level and occasionally headaches. No rashes, no oral ulcers. The initial episodes would last 24 hours and then resolve completely. This persisted for over 1 year and 7 months prior to his referral to rheumatology the fevers started coming every 2-3 weeks. The fever episodes and symptoms remained exactly the same with each episode. In between the episodes AA is completely symptomatic, active, growing well and gaining weight.

Past medical history

- Surgery for an inguinal hernia and a tonsillectomy. The tonsillectomy was performed per parents because of his frequent fevers, however there was no change in his fever pattern post surgery. AA has had microcytic anemia in the past and seen Hematology who felt the anemia was related to chronic inflammation. Has had elevated ESR and CRP in past.
- Family history
  - AA has a 24 year old brother with a similar history of persistent fevers, that occur monthly. Brother’s symptoms are persistent fevers and abdominal pain. There are 5 other children in the family, (4 boys, 1 sister) no other sibling have recurring fevers.
  - AA parents are from the Middle East, he and siblings were born in Milwaukee.
Case Study FMF

- Exam: Normal physical exam at the rheumatology clinic appt, was not experiencing an episode at the time
- Lab studies done: CBC, Chem panel, ESR, CRP, all in normal limits, but hs of elevated during flair
- Prior authorization initiated to the family health insurance carrier to obtain genetic testing for FMF
- Insurance approval obtained and buccal swab for genetic testing done
- AA positive for 2 MEFV gene mutations M680I and M694I. 24 year old brother with fever he then also tested and positive for MEFV gene mutation

Treatment

NSAIDs for fever and knee pain. Naproxen 100 mg bid
Colchicine started 0.3 mg (1/2 tab) bid
Side effects of Colchicine: potential bone marrow suppression, mild abdominal pain, mild diarrhea
Follow up: need CBC initially q 3 months, then 6 months, and urine twice a year

Treatment FMF

- Tylenol, ibuprofen for fever
- NSAIDS for joint pain/arthritis
- Prednisone 1 mg/kg/d if needed during flare
- Colchicine
  - Dose: 0.5-1 mg once or twice a day
  - Colchicine prevents episodes from starting, but does not treat an episode that has already started. If doses are missed or a patient stops taking the Colchicine the fever episodes will return
  - Side effects: abdominal pain, diarrhea, if occur can decrease dose,
  - Need to monitor CBC, LFTs, initially q 3 months, then q 6 months, need UA q 6 months

10% of patients do not respond or can not tolerate Colchicine, in these situations research has shown that Interleukin-1 agents maybe effective.

II-1 Biologic agents in FMF

- If patients unable to tolerate Colchicine or break through then, Biologic agents:
  - Rilonacept (Arcalyst) loading dose 4.4 mg/kg max dose 320 mg in 2 separate injections. Maintenance dose 2.2 mg/kg sub q weekly, max 160 mg
  - Anakinra (Kineret) 2mg/kg/day sub q injection
  - Canakinumab (Ilaris) 7.5-40 kg 2mg/kg subq injection q 4 weeks > 40 kg 150 mg q 4 weeks

Side effects of Biologic agents

- Mild injection site reactions,
- Flu like symptoms
- Immune suppressive agents increased risk of bacterial infections, viruses.
- Increased risk of TB, or reactivation of TB
- Black box warning of rare risk of malignancy
- No live immunizations, need yearly flu vaccine

Tumor necrosis factor associated periodic syndrome TRAPS

- Caused by a mutation in the TNFRSF1A gene
- Also known as Familial Hibernian Fever (FHF)
- 2nd most common inherited autoinflammatory disease
- Inherited autosomal dominant disease, if the abnormal gene is inherited from one parent, you can get the disease. As such one of the parents may be ill with TRAPS and possibly not realize it,
- The gene defect/mutation can develop spontaneously (not inherited) in a child.

Untreated FMF leads to Amyloidosis

- Amyloid is a protein that deposits in the organs of children who have chronic inflammatory diseases that are not well controlled. The most common organ involved is the kidney, but amyloid can deposit in the intestines, skin, and heart. Eventually, amyloid causes a loss of function, especially in the kidneys. If this occurs, dialysis or a kidney transplant might be necessary. Children who are properly treated with colchicine are safe from the risk of developing this life-threatening complication, but stopping treatment even for a short while can allow amyloidosis to occur. Patients with amyloidosis in the kidney will have high levels of protein in urine tests. Patients with FMF should have urine tests at least twice a year.
TRAPS: Autosomal Dominant

- Onset of symptoms start as early as age 3, but symptoms may start in mid childhood and usually by age 20
- The first cases were reported in patients from Irish-Scottish backgrounds, but has now been seen in all ethnic groups
- In mild cases may resemble symptoms of PFAPA
- TRAPS is due to a gene defect in a protein called tumor necrosis factor receptor, which leads to an increase of the patient’s normal inflammatory response.
- Like many of the other periodic fevers syndromes, infection, trauma, strenuous exercise, or psychological stress may trigger episodes

Symptoms seen in TRAPS

- Temps >38 that can last for weeks
- Migrating painful rash
- Abdominal pain
- Vomiting, diarrhea or constipation
- Conjunctivitis
- Periorbital edema
- Muscle/joint pain/arthritis
- Chest pain/pleurisy
- Enlarged spleen

Workup for TRAPS

- Keep fever log and accurate history of symptoms
- Complete Physical to rule out an infectious process
- CBC
- Inflammatory markers ESR, CRP, high during attacks, then return to normal between flares
- Once pattern established refer to rheumatology for review and genetic testing
- Like FMF, TRAPS left untreated can lead to Amyloidosis

Case Study TRAPS

- DW is a 10 year old male who was referred to rheumatology for reoccurring fevers, and oral ulcers occurring twice a month for 2 years. Fevers last 1-2 days, with highest temps 102-103. Fevers were minimally responsive to antipyretics. With these episodes he would feel fatigue and typically miss school for a few days. With one episode prior to being seen in rheumatology he was admitted for fevers, and chest pain and found to have a pericardial effusion on ECHO, normal EKG and spent a few days in ICU. Lab work demonstrated elevated ESR, CRP, all bacterial and viral studies were normal. In between episodes he feels well, attends school, plays sports and inflammatory markers return to normal.

Cutaneous symptoms of TRAPS
Case Study: TRAPS

- PE: at rheumatology clinic essentially normal. Not experiencing a fever episode at the time of clinic.
- Labs studies done ESR 19, CRP 0.5 Chem panel and CBC essentially normal, hx of elevated labs during flare
- Prior authorization obtained from health insurance carrier to do genetic fever panel
- DW positive for the heterozygous mutation for TNF SF-1 gene

Treatment

- Enbrel started at (0.8 mg/kg) 25 mg sub q injection weekly

Treatment for TRAPS

- Prednisone 1-2 mg/kg/ per day used a short term relief of symptoms if needed
- Etanercept (Enbrel) biologic agent that blocks TNF used at the onset of an attack or daily to prevent attacks
dose: 0.8 mg/kg q week sub q injection
- If no response to Etanercept or becomes refractory to Etanercept
- Anakinra (Kineret) interleukin 1 biologic agents
dose: 2mg/kg/day sub q injection
- Canakinumab (Ilaris) 7.5-40 kg 2mg/kg subq injection q 4 weeks
  > 40 kg 150 mg q 4 weeks

Hyperimmunoglobulin D Syndrome: HIDS

- Also called Mevalonate Kinase Associated Periodic Fever Syndrome
- Recessive inherited disease caused by Mevalonate Kinase gene MVK, from both parents.
- There are cases of spontaneous single-mutation dominant HIDS.
- 90% of children have symptoms before 1 year of age
- Most HIDS patients are Caucasian, live in western European countries and 60 percent are either Dutch or French.
- 80% of children have elevated IgD and IgA levels, not essential for dx however

HIDS

- Continuously high IgD values (more than 100 IU per milliliter) on 2-IgD lab tests done one month apart can help in the differential dx
- IgD level is not accurate in children under 2-3 years of age, plus 20% of HIDS patients never have elevated IgD, and elevated IgD is noted at times with other autoinflammatory diseases (but not as often as it is with HIDS)
- Over 80% of HIDS patients also have high IgA levels along with high IgD levels. During an attack, leukocytosis, high levels of C-reactive protein (CRP) and serum amyloid A are noted. Mevalonate aciduria is also noted in many cases.

Symptoms of HIDS

- Flares of HIDS symptoms or attacks usually begin with chills, then a quick rise in temperature that causes a fever for 3-7 days
- Symptoms last for 3-7 days and reoccur every 2-12 weeks
- The intensity of HIDS symptoms begins to taper off after a few days of the flare. The attacks are often triggered by vaccinations, minor trauma, stress, surgery or unknown causes.
- In between flares patients are free of symptoms, but it may take awhile for the joint pain and skin rash to fully disappear.
- Patients can sometimes be free of symptoms for many months or even years in some cases. Generally, patients have the greatest frequency of HIDS attacks during childhood through adolescence.

- Diffuse erythematous maculopapular rash, urticaria
- Conjunctivitis
- Oral ulcers
- Headaches
- Muscle/Joint pain, large joint arthritis
- Enlarged cervical nodes
- Abdominal pain, vomiting, diarrhea
- Fatigue/ malaise
Work up for HIDS

- Keep fever log
- Inflammatory markers ESR, CRP, high during a flare
- CBC, Neutrophils, and/or monocytes, and/or the overall WBC are also often high during a flare. This often leads to unnecessary treatment with antibiotics or a misdiagnosis as a recurrent virus or other infection.
- UA looking for high levels of mevalonic acid in the urine during a flare.

Case Study of HIDS

NL is a 15 year old male with long standing arthritis who was followed in the rheumatology clinic. Over the course of approximately 12 months he began having recurrent episodes of fevers, chills, abdominal pain, headaches, cervical adenopathy and flares of his underlying arthritis in both knees lasting 5-7 days. With many episode he was evaluated by his PMD of the rheumatologist, inflammatory markers ESR, CRP were elevated however no infectious cause was found. Due to these fevers he often had to hold his weekly Methotrexate treatment for his arthritis.

Additional labs were performed after several bout of these episodes to reveal an elevated IgD and IgA. Urine was tested as well and mevalonic acid was found. HIDS was suspected and genetic testing was done.

Treatment for HIDS

HIDS does not have a single treatment that works well for every patient

**Medications used**
- Tylenol, Ibuprofen, or NSAIDS such as Naproxen during the flare
- Prednisone 1 mg/kg/day
- Anakinra (Kineret) Interleukin-1 agent, used off label
- 2mg/kg/day sub q injection
- Canakinumab (Ilaris) Interleukin-1 agent is FDA approval
  - 7.5-40 kg 2mg/kg subq injection q 4 weeks
  - > 40 kg 150 mg q 4 weeks

Case Study HIDS

NL was found to be positive for Mevalonate Kinase gene MVK

**Treatment:**
- Methotrexate was stopped and he was started on Kineret
- Kineret 2mg/kg/day sub q injection

**Side effects:**
- Mild injection site reactions
- Flu like symptoms
- Immune suppressive agents increased risk of bacterial infections, viruses.
- Increased risk of TB or reactivation of TB
- Black box warning of rare risk of malignancy
- No live vaccinations, need yearly flu vaccine

Examination Findings Associated with Various Periodic Fever Syndromes

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<th>TRAPS</th>
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| Treatment | Captopril, 0.5 mg/day |
| NSAIDS   | Yes  | Yes  | Yes  | Yes   | Yes   |
| Black box warning | Yes | Yes |
| Live vaccinates | No | Yes |
Cost of oral medications

- Cost of Drugs
- Prednisone 5 mg tabs approximately $0.35-0.50 per tab
- Colchicine
  2010: FDA ordered generic colchicine off the market. URL Pharma raised its price from 10 cents per (generic) pill to $5 per pill

The approximate cost for Colchicine oral capsule 0.6 mg is around $466 for a supply of 100 capsules.
Coupoms available and assistance programs

Cost of Biologic agents

- Kineret 1 vial of 100 mg daily $41.10, monthly $1,230.00
- Enbrel 1 vial of 25 mg $82.5, monthly $2,475.00
- Ilaris monthly sub q injection $16,000
Patient assistants programs
- Enbrel: Embrel Support Card
- Ilaris: Eligible patients may pay no more than $50 per prescription with savings of up to $22,000 per calendar year; for additional information contact the program at 866-972-8315.
- Kineret: On TRACK program 1-866-547-0644

Kids speak out

- "The pain comes before the fever, I have pain all over and there's a rock in my belly" 5 y/o HIDs
- "It burns when people touch me or when things touch me" By/0 PFAPA
- "My legs are so very tired and my eyes are burning" 6y/0 TRAPS

Implications of Periodic Fever Syndromes

- Over time episodes of all of the periodic fever syndromes may affect the quality of life of the child and the family
- With each episode of a flare children may miss days of school, play dates and sports activities
- Due to repeat absences children may need school accommodations such as an IEP, 504
- Pain and frustration related to coping with a chronic illness
- Flares can be unpredictable causing disruption of family life

Implications of Periodic Fever Syndromes

- Parents miss work due to the ill child, and/or have to leave work early, arrive late bringing the child to the PMD for repeated evaluations
- Many parents have stress related to missed work days
- Challenges with health insurance companies getting genetic testing approved, challenges are seen with state and federal medical insurance as well as
- Challenges related to cost of medications and getting the medication payed for by health insurance companies
Resources for families

• Autoinflammatory Alliance
  autoinflammatory.org
• Systemic Autoinflammatory Disease Support
  saidsupport.org

References

• Padeh, S, Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome), UpToDate, December 2017.
• Autoinflammatory Alliance
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  saidsupport.org